REMARKS/ARGUMENTS

I. STATUS OF THE CLAIMS

Upon entry of this amendment, claims 42-52 are pending in this application and are presented for examination. Claims 1-41 have been canceled without prejudice. Claims 42, 46, and 48-49 have been amended. Support for the amendments to the claims is provided below. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

II. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 42-52 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description. To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

A. Inflammatory bowel diseases (IBDs)

In making this aspect of the rejection, the Examiner alleges that the specification and/or claims do not provide adequate written description to show possession of the entire genus of IBDs (*see,* Office Action at page 6). In particular, the Examiner contends that the specification does not provide sufficient identifying characteristics of members of the genus to provide evidence of possession of the entire genus of IBDs (*see, id*). In response, Applicant asserts that the specification clearly demonstrates to one of skill in the art that the present inventor was in full possession of the claimed invention at the time of filing.

As an initial matter, Applicant respectfully points out to the Examiner that IBD does not encompass a variety of diseases with different symptoms and clinical manifestations. Rather, there are *two* major IBD subtypes, Crohn's disease (CD) and ulcerative colitis (UC), which share similar demographic and epidemiological features (*see, e.g.,* the specification at page 1, lines 16-18). With regard to the Robbins *et al.* reference (Pathologic Basis of Disease, 2nd Ed. (1979)) cited by the Examiner, Applicant submits that CD is the only IBD subtype listed under the heading "ULCEROINFLAMMATORY DISEASE" on page 958. Likewise, UC is the only IBD subtype listed under the heading "INFLAMMATIONS" on page 982. Importantly,

with the exception of CD and UC, the other diseases listed on pages 958 and 982 of Robbins *et al.* are not considered IBD subtypes. In fact, Robbins *et al.* states that "there are many similarities between ulcerative colitis and Crohn's disease, and indeed there is a growing tendency *to consider them as a single entity - 'inflammatory bowel diseases (IBD)'*" (emphasis added; *see,* Robbins *et al.* at page 982, right column). As such, Robbins *et al.* does not describe any IBD subtypes other than the two major IBD subtypes, CD and UC.

Applicant asserts that the instant specification adequately describes sufficient identifying characteristics of CD and UC to demonstrate to one of skill in the art that the present inventor was in possession of the entire genus of IBDs. In particular, Table 1 on pages 51-59 of the specification provides numerous examples of gene products that are differently expressed in CD and/or UC cells. For example, GRO3, HNL, and COL6A3 are overexpressed in UC but not control or CD cells, whereas MMP-12 and elafin are overexpressed by about 4-fold in UC relative to CD cells. Table 1 also provides numerous examples of gene products that are underexpressed only in UC cells (*e.g.,* HDGF, anti-oxidant protein 2, metallothionein, MT1G, *etc.*), overexpressed only in CD cells (*e.g.,* SMT3H2, SMARCD1, DRAL, *etc.*), or underexpressed only in CD cells (*e.g.,* GNAS1, liver-specific bHLH-Zip transcription factor, IL2RG, *etc.*). As a result, Applicant submits that the specification provides an adequate description of sufficient identifying characteristics (*i.e.,* gene products that are differently expressed in CD and/or UC cells) of the entire genus of IBDs.

In view of the foregoing remarks, the disclosure of the instant specification is more than adequate to demonstrate to one of skill in the art that Applicant had possession of the presently claimed genus of IBDs at the time the application was filed. Accordingly, Applicant respectfully requests withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

B. Arrays

In making this aspect of the rejection, the Examiner alleges that the specification does not provide adequate written description to show possession of the claimed method of determining gene expression levels using an array comprising nucleic acid probes to determine

whether a test cell has an IBD or pre-IBD phenotype (*see,* Office Action at page 6). In response, Applicant asserts that the specification clearly demonstrates to one of skill in the art that the present inventor was in full possession of the claimed invention at the time of filing.

In order to expedite prosecution of the present case, Applicant has amended claim 49 to recite an array comprising nucleic acid probes of *12-40 nucleotides in length* that are *complementary* to and *hybridize under high stringency conditions* to the claimed gene products. Support is found, for example, from page 19, line 18 to page 20, line 3 and on page 45, lines 11-19 of the instant specification. As such, one of skill in the art would recognize that a nucleic acid probe present on the claimed array has a sequence which corresponds to the complement of a 12-40 nucleotide portion of a GRO3, HNL, MMP-12, elafin, or COL6A3 mRNA and hybridizes under high stringency conditions to that portion of the mRNA.

Additionally, the specification has been amended to provide the appropriate corresponding sequence identifier (SEQ ID NO:) for each GenBank Accession number set forth in Table 1. The enclosed Sequence Listing includes sequences corresponding to each GenBank Accession number in accordance with the requirements of 37 C.F.R. §§1.821 to 1.825. As set forth in MPEP § 2163.07(b), "[r]eplacing the identified material incorporated by reference with the actual text is not new matter." The specification at page 59, lines 19-20 explicitly incorporates all cited publications by reference. All of the sequences submitted in the Sequence Listing correspond to those published in GenBank at the time the present application was filed. Thus, the amendments to the specification and the Sequence Listing introduce no new matter and are fully supported by the specification as filed.

Applicant respectfully requests entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the above-named sequences, SEQ ID NOS:1-145, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk. The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

Since the specification provides the nucleotide sequence of each claimed gene product, Applicant asserts that one of skill in the art would appreciate that Applicant was in full possession of the nucleic acid probes present on the claimed array. In fact, the specification discloses art-recognized techniques for analyzing the nucleotide sequence of each claimed gene product to design nucleic acid probes that can be used on the claimed array. For example, the specification discloses that the sequence of each claimed gene product can be processed using an alignment algorithm or program such as BLAST or FASTA to identify stretches of non-homologous sequence (*see, e.g.,* the specification at page 14, line 3 to page 15, line 10). Nucleic acid probes having a sequence complementary to a portion of the non-homologous sequence can then be designed, tested for hybridization under high stringency conditions, and bound to a suitable substrate (*see, e.g.,* the specification at page 3, lines 19-37 and from page 19, line 18 to page 20, line 3).

In view of the foregoing remarks, the disclosure of the instant specification is more than adequate to demonstrate to one of skill in the art that Applicant had possession of the presently claimed invention at the time the application was filed. Accordingly, Applicant respectfully requests withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 42-52 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The Examiner alleges that the apparent contradiction between the preamble of claim 42 and the requirement that the IBD phenotypes of the test cell and control cell be known in order for their gene expression levels to be compared renders the claims indefinite (*see,* Office Action at page 9). The Examiner also alleges that it is unclear how the various expression levels of the claimed gene products are related to the determination of IBD in a cell (*see, id*). The Examiner further alleges that the phrase "the expression level of said gene product differs by at least a factor of two" is not clearly defined in claim 31 (*see, id*).

In order to expedite prosecution of the present case, Applicant has amended claim 42 to recite a method for determining whether a test cell has an IBD or pre-IBD phenotype comprising determining the expression level of GRO3, HNL, MMP-12, elafin, *and* COL6A3 in the test cell. The method further comprises comparing the expression level of each of these gene products to an expression level of the same gene product in a control cell and associating a difference in the expression level of at least one of these gene products from the expression level of the same gene product in the control cell with an IBD or pre-IBD phenotype in the test cell. Support is found, for example, on page 11, lines 28-31 and in Table 1 on pages 51-59.

As an initial matter, Applicant respectfully points out to the Examiner that the presently claimed method of determining whether a test cell has an IBD or pre-IBD phenotype requires that the expression level of the claimed gene products be determined in the test cell. In fact, the instant specification describes numerous art-recognized techniques for determining the expression level of the claimed gene products using, for example, Northern blot analysis, reverse transcription-polymerase chain reaction, in situ hybridization, or an array (*see, e.g.,* the specification at page 42, lines 2-24 and page 45, lines 11-19). As a result, contrary to the Examiner's allegation, the presently claimed method does not require that the IBD phenotype of the test cell be known in order for its gene expression profile to be compared to that of a control cell. Rather, it is the determination and comparison of the expression level of the claimed gene products in the test cell that permits the association of an IBD or pre-IBD phenotype with that test cell to be made.

With regard to the Examiner's allegation that it is unclear how the various expression levels of the claimed gene products are related to the determination of IBD in a cell, Applicant respectfully refers the Examiner to Table 1 on pages 51-59 of the instant specification. In particular, Table 1 provides data on the relationship between the expression level of each of the claimed gene products and the determination of IBD in a test cell. For example, Table 1 shows that GRO3, HNL, and COL6A3 are overexpressed in UC but not control or CD cells, whereas MMP-12 and elafin are overexpressed by about 4-fold in UC relative to CD cells. As a result, a determination that any one of these gene products is overexpressed in a test cell

compared to a control cell is useful for associating that test cell with an IBD or pre-IBD phenotype. Since GRO3, HNL, and COL6A3 are differentially expressed in UC but not control or CD cells, a determination that any one of these gene products is overexpressed in a test cell compared to a control cell is not only useful for associating that test cell with a UC or pre-UC phenotype, but is also useful for distinguishing a UC cell from a CD or normal cell. Similarly, a determination that either MMP-12 or elafin is overexpressed by about 3 to 4-fold in a test cell relative to a control cell is useful for associating that test cell with a CD or pre-CD phenotype and for distinguishing a CD cell from a UC or normal cell. As such, contrary to the Examiner's allegation, Applicant submits that it is clear how the expression level of each claimed gene product is related to the determination of an IBD or pre-IBD phenotype in a test cell.

Additionally, Applicant has amended claim 46 to recite that the expression level of at least one of the gene products differs from the expression level of the *same gene product* in the *control cell* by at least a factor of two.

In view of the foregoing remarks, the claims are definite and claim the present invention with particularity. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

IV. REJECTION UNDER 35 U.S.C. § 103(a)

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. MPEP § 2143. *See also, In re Rouffet,* 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (1999).

A. Dieckgraefe *et al.* in view of Nielsen *et al.*

Claims 42-52 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Alexander *et al.* (*Digestive Diseases and Sciences*, 41:660-669 (1996)) in view of Poulakkainen *et al.* (*Gastroenterology*, 114:A1064 (1998)). To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The Examiner alleges that it would have been *prima facie* obvious for one of skill in the art to use all of the known genes involved in IBD in an array to determine an IBD or pre-IBD phenotype based on the teachings of Alexander *et al.* and Poulakkainen *et al.* (*see,* Office Action at page 13). In response, Applicant asserts that the combination of references fails to teach all of the elements of the claimed invention. Moreover, one of skill in the art would not be motivated to combine the references.

As discussed above, Applicant has amended claim 42 to recite a method for determining whether a test cell has an IBD or pre-IBD phenotype comprising determining the expression level of GRO3, HNL, MMP-12, elafin, *and* COL6A3 in the test cell.

Applicant asserts that Alexander *et al.* discloses the differential expression of 8 protooncogenes (*i.e.,* H-*ras*, c-*myc*, c-*fos*, c-*jun*, *junB*, N-*myc*, c-*abl*, and c-*yes*) in colonic epithelial cells of IBD patients, but does not teach or suggest the differential expression of any of the claimed gene products in IBD relative to control cells. As a result, Alexander *et al.* fails to teach or suggest the presently claimed method in which the expression level of GRO3, HNL, MMP-12, elafin, *and* COL6A3 is determined. In fact, the Examiner has acknowledged that Alexander *et al.* does not specifically teach any of the claimed genes (*see,* Office Action at page 12).

Puolakkainen *et al.* does not supply the teaching that is clearly lacking in Alexander *et al.* Specifically, Puolakkainen *et al.* discloses the differential expression of stromelysin-2 (MMP-10), collagenase-3 (MMP-13), macrophage metalloelastase (MMP-12), and TIMP-3 in intestinal ulcerations, but does not teach or suggest the differential expression of each of the claimed gene products in IBD relative to control cells. As a result, given the absence of any teaching or suggestion in these references that GRO3, HNL, MMP-12, elafin, *and* COL6A3

are differentially expressed in IBD relative to control cells, none of these references, either alone or in combination, would read on the presently claimed method. In addition, one of skill in the art would not have been motivated to include all of the claimed gene products in the presently claimed method because it was not appreciated that their detection would lead to an improved determination of an IBD or pre-IBD phenotype based on the information provided by these references.

In view of the foregoing, the combined disclosures of Alexander *et al.* and Puolakkainen *et al.* do not render the presently claimed method obvious. Accordingly, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

B. Dieckgraefe *et al.* in view of Puolakkainen *et al.*

Claims 42-52 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dieckgraefe *et al.* (*Gastroenterology*, 114:A964-965 (1998)) in view of Puolakkainen *et al.* To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The Examiner alleges that it would have been *prima facie* obvious for one of skill in the art to use all of the known genes involved in IBD in an array to determine an IBD or pre-IBD phenotype based on the teachings of Dieckgraefe *et al.* and Poulakkainen *et al.* (*see,* Office Action at page 16). In response, Applicant asserts that the combination of references fails to teach all of the elements of the claimed invention. Moreover, one of skill in the art would not be motivated to combine the references.

As discussed above, Applicant has amended claim 42 to recite a method for determining whether a test cell has an IBD or pre-IBD phenotype comprising determining the expression level of GRO3, HNL, MMP-12, elafin, *and* COL6A3 in the test cell.

Applicant asserts that Dieckgraefe *et al.* discloses an oligonucleotide probe array that detected changes in the expression of different classes of genes in IBD specimens, but without reference to any particular genes in those classes. As a result, Dieckgraefe *et al.* fails to teach or suggest the presently claimed method in which the expression level of GRO3, HNL, MMP-12, elafin, *and* COL6A3 is determined. In fact, the Examiner has acknowledged that

Dieckgraefe *et al.* does not specifically teach any of the claimed genes (*see,* Office Action at page 16).

Puolakkainen *et al.* does not supply the teaching that is clearly lacking in Dieckgraefe *et al.* Specifically, Puolakkainen *et al.* discloses the differential expression of stromelysin-2 (MMP-10), collagenase-3 (MMP-13), macrophage metalloelastase (MMP-12), and TIMP-3 in intestinal ulcerations, but does not teach or suggest the differential expression of each of the claimed gene products in IBD relative to control cells. As a result, given the absence of any teaching or suggestion in these references that GRO3, HNL, MMP-12, elafin, *and* COL6A3 are differentially expressed in IBD relative to control cells, none of these references, either alone or in combination, would read on the presently claimed method. In addition, one of skill in the art would not have been motivated to include all of the claimed gene products in the presently claimed method because it was not appreciated that their detection would lead to an improved determination of an IBD or pre-IBD phenotype based on the information provided by these references.

In view of the foregoing, the combined disclosures of Dieckgraefe *et al.* and Puolakkainen *et al.* do not render the presently claimed method obvious. Accordingly, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

C. Dieckgraefe *et al.* in view of the instant specification

Claims 42-52 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dieckgraefe *et al.* in view of the instant specification. To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

The Examiner alleges that one of skill in the art would have been motivated to use the method of Dieckgraefe *et al.* and the known genes disclosed in the instant specification to determine an IBD or pre-IBD phenotype (*see,* Office Action at pages 18-19). The Examiner also contends that the genes disclosed in Table 1 of the instant specification are not novel and are well known for their role in IBD (*see,* Office Action at page 19).

As discussed above, Applicant has amended claim 42 to recite a method for determining whether a test cell has an IBD or pre-IBD phenotype comprising determining the expression level of GRO3, HNL, MMP-12, elafin, *and* COL6A3 in the test cell.

Applicant asserts that Dieckgraefe *et al.* discloses an oligonucleotide probe array that detected changes in the expression of different classes of genes in IBD specimens, but without reference to any particular genes in those classes. As a result, Dieckgraefe *et al.* fails to teach or suggest the presently claimed method in which the expression level of GRO3, HNL, MMP-12, elafin, *and* COL6A3 is determined. Again, the Examiner has acknowledged that Dieckgraefe *et al.* does not specifically teach any of the claimed genes (*see,* Office Action at page 18).

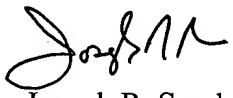
With regard to the instant specification, Applicant asserts that the Examiner has improperly characterized the sequences disclosed in Table 1 as being well known for their role in IBD. Although these sequences were known in the art, Applicant submits that the differential expression of gene products such as COL6A3 was never appreciated to have a role in IBD until the advent of the present invention. In fact, the instant specification is the first to show that GRO3, HNL, MMP-12, elafin, *and* COL6A3 are differentially expressed (*i.e.,* overexpressed) in IBD relative to control samples. As such, Applicant believes that the Examiner has impermissibly used an inventive feature of the claimed invention (*i.e.,* the discovery that the differential expression of GRO3, HNL, MMP-12, elafin, *and* COL6A3 can be used in a method for determining whether a test cell has an IBD or pre-IBD phenotype) in making this obviousness rejection. Accordingly, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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